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(54) Title: ANALGESIC COMPOSITIONS

(57) Abstract

Pharmaceutical formulations, particularly suitable for treating chronic and neuropathic pain comprise an opioid-potentiating amount of a CCK antagonist and an analgesic amount of an opioid in a pharmaceutically acceptable biphasic carrier comprising an organic phase comprising a glyceride derivative and a hydrophilic phase.

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ANALGESIC COMPOSITIONS

The present invention relates to pharmaceutical formulations suitable for treating pain, in particular, neuropathic pain and/or dysesthesia, and their preparation. In particular, the present invention relates to formulations comprising a cholecystokinin antagonist and an opioid.

Cholecystokinin (hereinafter 'CCK') has been implicated in a variety of physiological functions, one of which is the control of pain. CCK has been shown to have a heterogeneous distribution within the brain, with the greatest levels being found in the hippocampus, cerebral cortex, amygdala and olfactory lobes. The physiological role of central CCK receptors is still under investigation, but it has many of the features of a neurotransmitter. CCK has been found in regions of the brain known to be associated with pain modulation. Furthermore, mole-per-mole, CCK has been found to be much more potent than morphine in tests for analgesia.

However, at variance with these findings, are results of tests which imply that CCK may antagonise endogenous opiate action. (Faris et al. in Science 219 310-2 (1983)). There is evidence that exogenous CCK attenuates analgesia induced by morphine or release of endogenous opioids. These disparate findings and others imply that large doses of CCK induce a 'pharmacological' analgesia whereas small doses of the peptide produce physiological antagonism of opioid analgesics.

CCK also appears to play a rôle in the development of tolerance to opioid analgesia as blockade of CCK receptors has been shown to prevent tolerance to morphine. Hence, blockade of CCK receptors by CCK antagonists may reverse or prevent the development of opiate tolerance in patients, and also potentiates the analgesic effects of opioids. The present invention is therefore based on the thesis that blockage of CCK action may be an effective supplement to morphine (or other opioid) administration in the treatment of chronic pain. However, it is believed that this opioid facilitation is preferentially mediated by the central CCK type B receptors

since CCK-B antagonists seem to potentiate the analgesic effects of both opioids and non-opioids at the spinal level. Furthermore, facilitation of opiate-induced analgesia by CCK-B receptor antagonists seem to be restricted to μ -, rather than d-, opioid receptor-mediated antinociception.

5 Such μ -opioid agonists include morphine and hydroxymethyl fentanyl. However, potentiation of the analgesic effects produced by these opioids has also been observed with (relatively higher doses of) a CCK-A antagonist.

The present invention therefore generally relates to pharmaceutical formulations comprising an opioid-potentiating amount of a CCK antagonist together with an analgesic amount of an opioid. However, although the most popularly-used opioids such as morphine are not difficult to formulate, particularly for administration by injection, as they are water-soluble drugs, many CCK antagonists, particularly the preferred CCK antagonists to which

15 this invention relates, are relatively insoluble compounds which are therefore pharmaceutically incompatible with hitherto-known formulations of opiate drugs. Having therefore taken the step of appreciating the advantages to be gained by co-administration of an opioid with a CCK antagonist in a single formulation, it was then realised that such a formulation, or a satisfactory

20 carrier for the combination of active ingredients, was not available.

The present invention is therefore directed at solving this problem and provides a pharmaceutical formulation comprising

- (a) an opioid-potentiating amount of a CCK antagonist;
- (b) an analgesic amount of an opioid; and
- 25 (c) a pharmaceutically acceptable biphasic carrier comprising
 - (i) an organic phase comprising a glyceride derivative; and
 - (ii) a hydrophilic phase.

The organic phase may be either solid or liquid at room temperature

30 but preferably has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase. Examples are oils comprising a glyceride

which is liquid at room temperature and glyceride waxes having melting points in the range 35-80°C.

The organic phase may therefore comprise, for example, soya bean, safflower, sesame, rapeseed, peanut, olive, cotton seed or fish oils. Preferably, soya bean and/or safflower oils are chosen, alone or in combination with glycerine. Alternatively, the organic phase may comprise waxes such as full and/or partial glycerides of fatty acids. Preferably, such waxes are triglycerides and partial glycerides of unsaturated C₁₂₋₁₈ fatty acids such as, for example, Witpsol H15 or W25.

10 The hydrophilic phase may itself be aqueous, or may be anhydrous but take in and/or dissolve in water in vivo. In the case of formulations for intravenous use, the hydrophilic phase preferably has a viscosity of from 2500-7500cp (2% aqueous at 20°C), more preferably around 4000cp. Such ingredients may also be added to prevent or reduce coalescence of oily droplets of the organic phase. In the case of solid formulations such as tablets and suppositories, the hydrophilic phase is gel-forming and incorporates the opioid in the gel, and also forms a matrix for incorporating the CCK antagonist plus glyceride. The hydrophilic or aqueous phase may therefore comprise a pharmacologically and pharmaceutically acceptable polymer or salts thereof which may be selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl cellulose, other cellulose derivatives which are water-swellaable such as hydroxypropylmethyl-cellulose and hydroxyethyl cellulose or other water-swellaable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble polymers such as lactose.

In the formulation, the organic and hydrophilic phases may be separated or may be combined, for example, to form an oil-in-water emulsion. Preferred such emulsions therefore comprise:

- 30 (i) an oil phase comprising a glyceride derivative; and
(ii) an aqueous phase optionally comprising a buffer whereby the

emulsion has a pH of from 6.5 to 7.5 and optionally comprising an isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

When the carrier is in the form of an emulsion, the average particle size of the resultant emulsion is preferably in the range 0.2 to 3.0 μ m, more preferably around 1 μ m.

Optionally, an emulsifying agent and/or surfactant may be incorporated into the carrier. A suitable surfactant is a sorbitan derivative such as the polysorbates, for example polysorbate 80, or sorbitan mono-oleate, and the poloxamers such as Pluronic F38. Suitable emulsifying agents include egg yolk lecithin, egg yolk phospholipids such as phosphatidyl choline and the like.

To adjust the pH, a suitable pH adjuster (i.e. an acidifying or alkalising agent) is used such as hydrochloric acid or sodium hydroxide, or a buffer such as a phosphate buffer system. Preferably, the pH is adjusted to 7-7.5, more preferably, it is close to neutral (pH = 7).

Liquid formulations may also comprise an isotonicity regulator to ensure that the aqueous phase thereof is or remains isotonic to blood plasma. Examples of such isotonicity regulators include dextrose, glucose, mannitol, sorbitol, glycerol and sodium chloride.

Other hydrophobic or hydrophilic components may be included in the formulation such as, particularly in the case of suppositories, a thickener or gelling agent for the organic phase such as hydrophobic silicon dioxide or silica; lubricants; particularly in the case of tablet formulations, such as magnesium stearate, stearic acid, talc and LUBITROL, preferably magnesium stearate. Optional other ingredients include colouring or flavouring agents, release agents, pore-forming agents, stabilisers, and fillers or diluents such as lactose, calcium phosphate or carbonate, microcrystalline cellulose and the like, and antioxidants.

Also, in the case of tablets, a coating may be applied such as waxes, fatty alcohols, water-insoluble cellulose derivatives, other water-insoluble polymers such as polymers or copolymers of acrylates and/or methacrylates

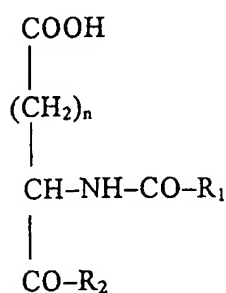
(eg. EUDRAGIT), ethylcellulose, cellulose acetate, shellac, hydrogenated vegetable oils and the like. Such a coating may provide the mechanism to enable controlled release of the opioid. Such a coating may optionally include a plasticizer or film enhancer such as monoglycerides, phthalates, 5 sebacates, citrates, castor oil and the like.

Preferably, the CCK antagonist is incorporated into the organic phase, and more preferably into the glyceride derivative, and the opioid analgesic is incorporated into the hydrophilic phase. However, the present invention does not preclude having components (a) and (b) present in any 10 combination in any phase of the carrier.

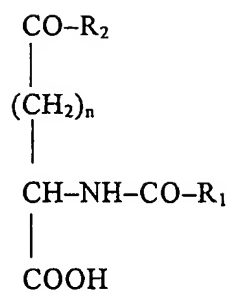
The components are preferably present within the following ranges of ratios: 10:1 to 1:5, respectively (i):(ii); and 1:2 to 1:40, respectively (a):(b).

The opiate drug may be selected from those which are effective analgesics and particularly those which need to be administered at relatively 15 high or increasing doses. Examples include morphine, or a salt thereof such as the sulphate, chloride or hydrochloride, or other 14-hydroxymorphinan opioid analgesics such as naloxone, meperidine, butorphanol or pentazocine, or morphine-6-glucuronide, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine or fentanyl, or a salt of any of 20 these.

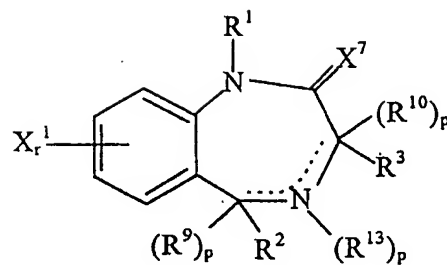
The CCK antagonist may be selected from any of those which potentiate the analgesic effects of the opioid chosen and/or which reverse or prevent patient tolerance thereto. For example, CCK antagonists include those of formulae (I)-(IV) which are defined, respectively, in (I) US 4791 215; 25 (II) EPs 167 919 and 284 256; (III) EP 405 537; and (IV) J. Med. Chem. 34 1508 (1991), which are herein incorporated by reference in their entirety.



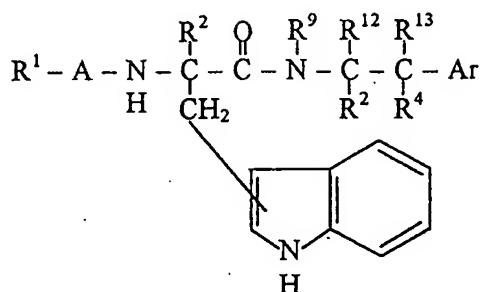
(Ia)



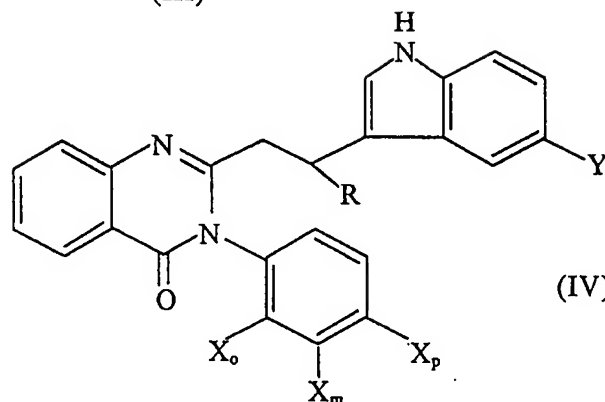
(Ib)



(II)



(III)



(IV)

Preferred CCK antagonists are selected from those described in European patents specifications nos. 167 919; 284 256; 508 796; 652 871; 411 668; 421 802; and 617 621, which are herein incorporated by reference

5 in their entirety. Particularly preferred CCK antagonists include devazepide (also known as MK-329), namely, 3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (a CCK-A antagonist); L-365,260, namely 3R-3-(N'-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (a CCK-B

antagonist); and so-called second generation compounds such as L-369,466, namely N-[1,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-(1,2,4-oxodiazol-5-one)phenyl]urea, L-741,528, namely (-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[indan-5-yl]urea and [N-[(3R)-5-(3-azabicyclo[3,2,2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl) urea] (L-740,093, a CCK-B antagonist described in Molecular Pharmacol. 46 943-8 (1994)). Especially preferred are the CCK-B antagonists, in particular L-365,260 and the previously-mentioned second generation compounds.

The formulations of the present invention are preferably sustained-, slow- or continuous-release (S.R.) solid formulations, or emulsions for injection. S.R. formulations may be in the form of a suppository or tablet, for example.

The formulations of the present invention are particularly suitable for treating chronic and neuropathic pain. Nerve damage arising from either trauma or disease affecting peripheral nerves leads to abnormal pain states referred to as neuropathic pain. Such pain may be long-lasting and continue for extended periods after the initial injury has healed. Individuals afflicted with neuropathic pain show a marked sensitivity to nociceptive stimuli, indicative of a lowered nociceptive threshold (hyperalgesia). Moreover, there is also a perception of normally innocuous stimuli being nociceptive, a state referred to as allodynia.

In particular, these formulations are suitable for treating patients with spinal cord injury. They prevent tolerance to the opioid analgesic and eliminate the need to increase doses of opioid to clinically unacceptable levels. However, they are also useful in enhancing opioid analgesia in non-pathological pain states, and the anxiolytic (anti-anxiety or anti-panic) effects of some CCK antagonists is a particularly beneficial additional effect.

A suitable daily dose of CCK antagonist in these formulations would preferably be in the range 0.5 to 300mg per day, such as 1 to 100mg/day

(oral or via suppository) or 1 to 300mg/day (i.v.). Preferably, for MK-329, the dose would be 1-10mg/day (5-10 mg/day orally or 1-3mg/day i.v.); for L-365,260, the dose would be 10-100mg/day orally (5-10mg/day orally or 10-300 mg/day i.v.); and for 'second generation' CCK antagonists, 1-2mg/day
 5 (oral) or 0.5-1.5 mg/day (i.v.).

The present invention will now be illustrated by the following non-limiting examples:

Example 1 : Intravenous Emulsions

	(a)	L-740,093 (active (a))	0.00025g
10		Morphine sulphate (active (b))	0.010g
		Soya bean oil (i)	0.4000ml
		Phosphatidyl choline (emulsifier)	0.0240g
		Pluronic F 68 (surfactant)	0.0040g
		Water (ii)(adjusted to pH 7	2ml
15		to 7.5 and made isotonic with sorbitol q.s.)	

The injection is prepared using aseptic techniques and sterile materials. The MK-329 is dispersed in the soya bean oil and the morphine is dissolved in the water. The two phases are emulsified using standard
 20 pharmaceutical technology and stabilised by the phosphatidyl choline and Pluronic F 68. The amount of morphine sulphate may be altered to provide a range of potencies. A 2ml bolus intravenous injection may be administered every four hours, or the formulation may be incorporated into the reservoir of an analgesic self-administration device.

25			1g ~ 1ml
	(b)	MK-329 (a)	0.0015g
		Fentanyl citrate (b)	0.0024g
		Soya bean oil (i)	0.0993g
		Safflower oil (i)	0.0993g
30		Phosphatidyl choline (emulsifier)	0.0125g
		Glycerine	0.0200g

Water (qs 1 ml) (ii) 0.7665g

qs 0.1 N NaOH to adjust pH to 7.0 - 7.5

The ingredients were mixed together and emulsified in a similar manner to that described above in Example 1(a).

5 Example 2 : Intravenous Infusions

	(a)	MK-329 (a)	0.015g
		Morphine sulphate (b)	0.100g
		Cottonseed oil (i)	200ml
		Polysorbate (surfactant)	1.6g
10		Fractionated egg	
		phospholipids (emulsifier)	12.000g
		Hydroxypropyl methylcellulose (ii)	5.000g
		Water (ii) (adjusted to pH 7	1000ml
		to 7.5 and made isotonic	
15		with sorbitol)	

The MK-329 is dispersed in the oil phase and the fentanyl citrate is dispersed in the aqueous phase. The emulsion is formed using standard pharmaceutical techniques. One litre of emulsion may be administered intravenously over a 24-hour period. The amount of morphine may be
 20 adjusted to allow a range of doses, depending on the response of individual patients.

	(b)	L-365,260 (a)	0.03g
		Morphine sulphate (b)	200mg
		Soya bean oil (i)	100g
25		Egg yolk lecithin (emulsifier)	12g
		Glycerine (i)	25g
		Gelatine (ii)	50 g
		Water q.s. to (ii)	1 litre

All the ingredients are emulsified together, except the gelatine, at
 30 80°C. The temperature is reduced to about 40°C and the gelatine added.

Example 3 : S.R. Suppository

	Butorphenol tartrate (b)	30mg
	MK-329 (a)	12mg
	Hydroxypropyl methylcellulose (ii)	300mg
	Aerosil R972* (thickener)	100mg
5	Witepsol H15 or ((i), glycerides)	
	Witepsol W25 to	2500mg
	(Hydrophobic silica)	

The MK329 and Aerosil are added to molten Witepsol. The butorphenol is blended with hydroxypropyl methylcellulose and then added to the Witepsol mixture. The mixture is poured into 3 ml moulds and shock cooled to room temperature.

Example 4 : Coated S.R. Tablet

	(a) <u>Core</u>	
	MK-329 (a)	0.015g
15	Suppocire DM (((i), glyceride*)	0.100g
	Levorphanol tartrate (b)	0.006g
	Crosslinked polyvinyl pyrrolidone (PVP) (ii)	0.010g
	Lactose (ii)	0.175g
20	<u>Coating</u>	
	Cellulose acetate	0.020g
	(b) <u>Core</u>	
	Dihydrocodeine tartrate (b)	180mg
	Suppocire DM ((i), glyceride)	100mg
25	L-741,528 (a)	4mg
	Polyvinylpyrrolidone (PVP) (ii)	40mg
	Lactose (ii)	123mg
	Magnesium stearate (lubricant)	1.5mg

* Suppocire DM is a mixture of hemi-synthetic glycerides of C₁₂₋₁₈ saturated with fatty acids.

Coating

	Hydroxypropyl methylcellulose (ii)	14.45mg
	Triethyl citrate (plasticiser)	6.9mg
	30% aqueous dispersion	
	ethyl cellulose	17.21mg
5	Purified water	q.s.

The dihydrocodeine tartrate is dispersed in molten Suppocire which is cooled with constant stirring to give a granular product. These granules are blended with other materials and tableted.

Example 5 : S.R. Tablet

10	L-740,093 (a)	0.002g
	Suppocire DM ((i), glyceride)	0.100g
	Dihydrocodeine tartrate (b)	0.180g
	Magnesium stearate (lubricant)	0.003g
	Hydroxypropyl methyl cellulose (ii)	0.250g
15		<hr/> 0.548g

The L-740,093 is dissolved in molten Witepsol W25 at 50-60°C. The resulting liquid is atomised into a chamber containing chilled nitrogen (gas) at about 10°C. Spherical particles produced thereby are in the range 80-120 μm . These are then blended with the dihydrocodeine tartrate and remaining excipients to produce a powder which is tableted by standard techniques.

Example 6 : S.R. Capsules

	L-369,466 (a)	0.0004g
	Morphine sulphate (b)	0.100g
25	Suppocire DM ((ii), glyceride)	0.200g
	Sodium alginate (i)	0.200g

The L-369,466 and morphine are incorporated into molten Witepsol. Granules or spheroids are produced by standard pharmaceutical techniques, then blended with the sodium alginate before filling into capsule shells. The amount of morphine in each capsule, for once daily administration, can be changed within the range 30mg to 150mg.

CLAIMS

1. A pharmaceutical formulation comprising
 - 5 (a) an opioid-potentiating amount of a CCK antagonist;
 - (b) an analgesic amount of an opioid; and
 - (c) a pharmaceutically acceptable biphasic carrier comprising
 - (i) an organic phase comprising a glyceride derivative; and
 - (ii) a hydrophilic phase.
- 10 2. A pharmaceutical formulation according to claim 1, wherein the organic phase (i) has a solubilising capacity for the CCK antagonist in excess of 5mg per gram of organic phase.
3. A pharmaceutical formulation according to claim 1 or 2, wherein the organic phase comprises an oil selected from soya bean, safflower, sesame,
15 rapeseed, peanut, olive, cotton seed and fish oils, alone or in combination with glycerine and/or a wax selected from full and/or partial triglycerides of fatty acids.
4. A pharmaceutical formulation according to any one of claims 1 to 3, intended for intravenous use, wherein the hydrophilic phase is aqueous and
20 has a viscosity of from 2500-7500cp at 20°C.
5. A pharmaceutical formulation according to any one of claims 1 to 3, intended for use as a solid formulation, wherein the hydrophilic phase is gel forming, incorporates the opioid in the gel and forms a matrix incorporating the CCK antagonist and the glyceride derivative.
- 25 6. A pharmaceutical formulation according to any one of the preceding claims wherein the hydrophilic phase comprises a pharmacologically and pharmaceutically acceptable polymer or salt thereof selected from proteins such as gelatine, hyaluronic acid, alginic acids or salts thereof such as sodium alginate, carboxymethylcellulose (optionally cross-linked), methyl
30 cellulose, other cellulose derivatives which are water-swellaable such as hydroxypropylmethylcellulose and hydroxyethyl-cellulose or other water-

swellable polymers such as polyvinyl pyrrolidone (PVP) or water-soluble polymers such as lactose.

7. A pharmaceutical formulation according to any one of the preceding claims, wherein the carrier is in the form of an oil-in-water emulsion.

5 8. A pharmaceutical formulation according to claim 7, wherein the oil-in-water emulsion comprises

(i) an oil phase comprising a glyceride derivative; and

(ii) an aqueous phase optionally comprising a buffer whereby the emulsion has a pH of from 6.5 to 7.5 and optionally comprises
10 an isotonicity regulator whereby the aqueous phase is made isotonic to blood plasma.

9. A pharmaceutical formulation according to claim 7 or 8 wherein the average particle size of the emulsion is from 0.2 to 3.0µm.

10. A pharmaceutical formulation according to any one of claims 7 to 9
15 further comprising an emulsifying agent, a surfactant and/or a pH adjuster.

11. A pharmaceutical formulation according to any one of the preceding claims, wherein the CCK antagonist (a) has been incorporated into the organic phase (i) and the opioid analgesic (b) has been incorporated into the hydrophilic phase (ii).

20 12. A pharmaceutical formulation according to any one of the preceding claims, wherein the ratio of component (i) to component (ii) is within the range of 10:1 to 1:5 by weight.

13. A pharmaceutical formulation according to any one of the preceding claims, wherein the ratio of component (a) to component (b) is within the
25 range of 1:2 to 1:40 by weight.

14. A pharmaceutical formulation according to any one of the preceding claims, wherein the CCK antagonist (a) is selected from:

3S-(-)-(1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

30 3R-3-(N'-(3-methylphenyl)ureido)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

- N-[1,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-N'-[3-(1,2,4-oxodiazol-5-one)phenyl]urea;
(-)-N-[2,3-dihydro-5-(4,4-dimethylpiperidin-1-yl)-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-[indan-5-yl]urea; and
- 5 [N-[(3R)-5-(3-azabi-cyclo[3.2.2]nonan-3-yl)-2,3-dihydro-1-methyl-2-oxo-1H-1,4-benzodiazepin-3-yl]-N'-(3-methylphenyl)urea].
15. A pharmaceutical formulation according to any one of the preceding claims, wherein the opioid (b) is selected from morphine, codeine, or a salt thereof, and 14-hydroxymorphinan opioid analgesics and salts thereof.
- 10 16. A pharmaceutical formulation according to any one of the preceding claims as a solid formulation, an injectable emulsion, suppositories or tablets.
17. A pharmaceutical formulation according to any one of the preceding claims in unit dosage form suitable for the delivery of 0.5 to 300mg per day
- 15 of CCK antagonists to a patient in need thereof.
18. A pharmaceutical formulation according to claim 17 in unit dosage form suitable for oral use or use as a suppository for the delivery of 1 to 100mg per day of CCK antagonist to a patient in need thereof.
19. A pharmaceutical formulation according to claim 17 in unit dosage
- 20 form suitable for intravenous use for the delivery of 1 to 300 mg per day of CCK antagonist to a patient in need thereof.
20. A method of treating chronic and neuropathic pain comprising administering to a patient in need thereof a pharmaceutical formulation according to any one of the preceding claims.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/03076

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/55 A61K9/107 A61K9/20 //(A61K31/55, 31:485)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 791 215 A (ROVATI ET AL.) 13 December 1988 cited in the application see column 1, line 1 - line 44 see column 31, line 4 - line 45 ---	1-20
A	GB 1 564 039 A (BERGER) 2 April 1980 see the whole document ---	1-20
A	EP 0 222 614 A (ELI LILLY AND COMPANY) 20 May 1987 see the whole document ---	1-20
A	EP 0 391 369 A (YISSUM RES. DEV. COMP. HEBREW UNIVERS. JERUSALEM) 10 October 1990 see page 8; example 2 -----	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

9 February 1999

Date of mailing of the international search report

16/02/1999

Name and mailing address of the ISA

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Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/03076

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 98/03076

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